Remarks

Claims 34, 36, 38-40, and new claim 50 are pending in this application. Claims 35, 37, and 48-49 are canceled without prejudice to Applicants' right to pursue the subject matter recited by them in one or more divisional, continuation, or continuation-in-part applications. New claim 50 recites a more specific dose of DCL, and is entirely supported by the specification and claims as originally filed. *See, e.g.*, Specification, page 14, lines 15-16. No new matter has been introduced.

As requested by the Examiner, a complete copy of Brandes *et al. J. Natl. Cancer Institute*, 86(10): 770-775 (1994) ("Brandes") is enclosed herein.

Applicants respectfully submit that all of the pending claims are allowable for the following reasons.

A. The Rejections Under 35 U.S.C. § 112, ¶ 2, Should Be Withdrawn

On page 2 of the Office Action, the rejection of claims 35, 36, 37, 48 and 49 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter of the invention, is maintained. Applicants respectfully traverse these rejections.

First, it is alleged that claims 35, 37, 48 and 49 are indefinite because these claims do not recite "further procedural steps." Office Action, page 2. Although Applicants respectfully disagree with the Examiner's requirement that these claims have "further procedural steps," these dependent claims are canceled to expedite the prosecution of the remaining claims, including claim 34 from which the canceled claims depended. In view of the cancellation of these claims, Applicants respectfully request that this rejection be withdrawn.

Second, it is alleged that claim 36 is indefinite because the claim "does not define which particular cancer is to be avoided." Office Action, page 2. In response, Applicants point out that claim 36 does not recite avoiding cancer. Instead, it relates to a patient population by reciting a method of treating urticaria in a patient who has higher than normal propensity for or incidence of cancer. As a result, Applicants respectfully point out that claim 36 is clear. Furthermore, the term "cancer," although it may have a number of sub-types, is a well-defined term that is understood and known to those of ordinary skill in the art, thus, the claim is clear. To the extent the Examiner believes the term "cancer" is broad, Applicants submit that the "[b]readth of a claim is not equated with indefiniteness," Applicants respectfully

request that the rejection of claim 36 be withdrawn. MPEP § 2173.04, citing *In re Miller*, 441 F.2d 689, 693 (C.C.P.A. 1971).

B. The Rejections Under 35 U.S.C. § 112, ¶ 1, Should Be Withdrawn

On pages 3-4 of the Office Action, claim 37 is rejected under 35 U.S.C. § 112, ¶1, as allegedly not enabled. Applicants respectfully traverse. However, in order to expedite prosecution of the remaining claims, claim 37 has been canceled. In view of the cancellation of claim 37, this rejection is moot. Consequently, Applicants respectfully request that this rejection be withdrawn.

C. The Rejection Under 35 U.S.C. § 103(a), over Berkow and Villani, Should Be Withdrawn

On pages 4-6 of the Office Action, claims 34, 36, and 38-40 are rejected as allegedly obvious over Berkow *et al.*, *The Merck Manual of Diagnosis and Therapy*, 16th Ed., pp 332-334 (1992) ("Berkow") in view of Villani. In particular, it is alleged that Berkow discloses that symptoms of urticaria can be relieved with an antihistamine, and Villani discloses DCL and related compounds are antihistamines, thus the claims are obvious. Applicants respectfully traverse the Examiner's interpretation of these references and the rejection.

In their previous response, Applicants pointed out that the claims are not obvious because Berkow merely discloses that symptoms of acute urticaria *usually can* be relieved with oral anti-histamines, such as diphenhydramine, hydroxyzine, or cyprohependine (all of which are first generation antihistamines), but does not disclose or suggest the use of any second generation non-sedating antihistamines, much less DCL, to treat urticaria. Response of August 20, 2004, page 7. Applicants also pointed out that other prior art references, by teaching that not all antihistaminic agents can be used to treat urticaria, render it impossible to conclude that Berkow's teaching can be extrapolated to all antihistaminic agents. *Id.* pages 7-8.

Apparently misinterpreting Applicants' argument, the Examiner responds by contending that Berkow's teaching is not limited to the three exemplary antihistaminic agents it discloses. Office Action, page 6. In addition, the Examiner argues that Berkow's teaching is "much longer and more nuanced" than Applicants suggest, because Berkow itself discloses that "the listed agents useful for treatment do not always work in every patient." *Id.* This is precisely Applicants' point: the

pending claims are not obvious because Berkow does not disclose the use of DCL for the treatment of urticaria, and does not even suggest that all antihistaminic agents are effective in treating urticaria. It appears that the Examiner is in complete agreement with Applicants that Berkow does not render obvious the treatment of urticaria with all known antihistamines. In fact, Berkow is nothing more than an invitation to experiment with antihistamines. As the Examiner is well aware, an invitation to experiment is not a proper basis for an obviousness rejection. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1380 (Fed. Cir. 1986). For these reasons, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. § 103 should be withdrawn.

In addition to the evidence of non-obviousness discussed above, the Examiner must, as he admits, consider the art as a whole. *See, e.g., Manual of Patent Examining Procedure*, § 2141 (citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966)). In other words, neither Berkow nor Villani can be considered in a vacuum. In this regard, Villani does not remedy the deficiencies of Berkow because it does not suggest the use of DCL to treat urticaria for at least two reasons.

First, the crude assay provide by Villani at columns 8-9 does not even provide confirmation that the compounds tested would be useful against allergic disorders, much less urticaria. To this end, Applicants submit herewith a declaration by William W. Storms, M.D. ("Storms Declaration"), which was submitted in connection with the prosecution of Applicants' corresponding European patent application.[1]

As the Examiner will see, Dr. Storms provides that the reduction of histamine-induced paw edema is not an indicator of whether a compound can be used to treat allergic disorders. This is because, while agents that selectively prevent histamine binding to H_1 histamine receptor ("H_1 antagonists") may be used for the treatment of allergic disorders, agents that prevent histamine binding to other histamine receptors ("H_2 or H_3 antagonists") may not. *See* Storms Declaration, ¶ 6-7. Yet, certain H_2 and H_3 antagonists were known to reduce histamine-induced paw edema in rodents. *Id.*, ¶ 8-9. Therefore, the disclosure of Villani that DCL reportedly reduces the histamine-induced paw edema in mice would not have suggested to those

[1] For the Examiner's convenience, Applicants point out that the EPO has decided to grant claims in this application.

of ordinary skill in the art that DCL can be used for the treatment of allergic disorders, much less urticaria as claimed herein.

Further, and perhaps more importantly, DCL was, at the time of the claimed invention, known to be a member of a group of molecules that caused serious adverse effects. *See*, Storms Declaration, ¶ 12-15. Similarly, since DCL is a metabolite of loratadine, there were concerns that DCL could be associated with tumor growth or personality changes. *See Id.*, ¶ 17. This knowledge would certainly have cut against an alleged suggestion by the combination of Villani and Berkow that DCL could be used to treat urticaria. Applicants refer to ¶ 12-17 of Storms Declaration. Thus, even if Villani and Berkow are combined, when considered with the knowledge of the potential side effects of DCL (*e.g.*, cardiac side effects and potential tumor promotion), an allegation of obviousness is legally flawed.

In sum, neither Berkow nor Villani, either alone or in combination, suggest the use of DCL to treat urticaria. Further, when the references are considered with the art as a whole, it is clear that their teachings do not overcome the art that taught away from the use of DCL as an antihistamine. In fact, Villani and Berkow add nothing to motivate one of ordinary skill in the art to look at beyond these teaching away and to using DCL. For these reasons, the rejection under 35 U.S.C. § 103(a) over Berkow in combination with Villani should be withdrawn.

Applicants also submit that the claims are not obvious for the reasons set forth in their response of August 20, 2004, which is incorporated herein by reference in its entirety.

D. The Rejection Under 35 U.S.C. §103 over Swinyard, Villani, and Brandes, Should Be Withdrawn

On pages 7-8 of the Office Action, claims 34-40, 48, and 49 are rejected for as allegedly obvious over the excerpts from *Remington's Pharmaceutical Sciences* (1990) ("Swinyard (I) and (II)"), in view of Villani and Brandes. In particular, it is alleged that the claims are obvious because: (1) Swinyard (II) discloses the use of H_1-antagonists in the treatment of urticaria, and also discloses azatadine maleate, which has a structure according to the Examiner similar to loratadine and DCL, as one of the antihistamines; (2) Swinyard (I) discloses that not all antihistamines cause problems with P450 enzyme metabolism, and thus selection of non-problematic antihistamine is an effective way to avoid the side effects; and (3)

Villani discloses that DCL is an antihistamine with low CNS-related side effects.[2] Applicants respectfully traverse this rejection.

Although Swinyard (II) discloses that antihistamines can be used to treat urticaria and other diseases, it does not disclose that DCL can be used for that purpose. In addition, Swinyard (II) lists a number of side effects caused by the antihistamines. Swinyard (II), page 1124, right column. More important, Swinyard (II) teaches that while "enormous number of clinical conditions for which antihistaminic drugs have been suggested," these drugs "vary from *effective* to *ineffective* in these conditions." *Id.* at last paragraph (emphasis in original). Thus, Swinyard (II) recognizes "the complex therapeutic problem that confronts the thoughtful physician in the selection of antihistamine." *Id.* This clearly teaches that no generalization can be made regarding a particular antihistaminic agent's efficacy in treating a particular disease, based on a different agent's efficacy. Therefore, Swinyard (II) would not have suggested that antihistamines in general, much less DCL, can be used for the treatment of urticaria.

Furthermore, the Examiner appears to suggest that Swinyard (II) would have provided the required motivation because it discloses azatadine maleate as one of the antihistaminic agents, and azatadine maleate has a structure similar to loratadine and DCL. Office Action, page 7. But as Applicants repeatedly pointed out in their previous responses and briefs on appeal, the disclosure of an antihistaminic compound structurally similar to DCL would not have motivated the use of DCL. This is because antihistaminic agents structurally similar to DCL (*e.g.*, loratadine, terfenadine, and astemizole) were thought to be associated with cardiac side effects, personality change, or tumor promotion. *See, e.g., Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed. (1996), page 590, a copy of which is enclosed herein; *see also* Storms Declaration, ¶ 12-17. As a result, one of ordinary skill in the art would have in fact been taught away from the claimed invention.

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[2] It is unclear as to why Brandes is also cited for the rejection. As the Examiner recognizes, Brandes discloses that loratadine promotes the growth of certain tumors, which substantiates the non-obviousness of the claims because those of ordinary skill in the art would not have been motivated to use DCL, for fear that it, too, would cause the same tumor promotion. Moreover, the Examiner asserts that the data disclosed in the specification regarding tumor promotion is "at best incomplete." Not only does the Examiner fail to provide a factual or scientific support for this allegation, but the allegation, even if true, is simply irrelevant to the non-obviousness of the claims.

In this regard, Applicants again refer to Storms Declaration. In the declaration, Dr. Storms confirms that safety of a drug used to treat non-life-threatening diseases, such as allergic disorders, is of paramount importance, because the risks associated with the treatment cannot be outweighed by the relief of relatively trivial discomfort. *See* Storms Declaration, ¶ 10-11. In addition, Dr. Storms attests to the fact that prior to the effective filing date of this application, *i.e.*, December 30, 1994, those of ordinary skill in the art would not have motivated to use DCL for the treatment of allergic disorders because prior known antihistamines that have structures similar to DCL, such as loratadine, terfenadine, and astemizole, were all known to cause serious adverse effects. Id., ¶ 12-22. Consequently, Applicants respectfully submit that the Swinyard (II)'s disclosure of azatadine maleate would not have motivated those of ordinary skill in the art to use DCL, much less use it for the treatment of urticaria.

Swinyard (I) and Villani add nothing to the substance of the rejection. As the Examiner notes, Swinyard (I) discloses that only certain H_2-antagonists cause cardiac side effects, and the problem can be negated by selecting the right H_2-antagonist. Applicants agree. But in view of the fact that other antihistamines structurally similar to DCL were thought to be associated with cardiac side effects, Applicants submit that those of ordinary skill in the art would not have selected DCL. In addition, since Villani merely discloses the crude antihistaminic activity of compounds it discloses, it does not even provide any suggestion that its compounds, much less DCL, can be used for the treatment of urticaria. *See* Storms Declaration, ¶ 6-9. Consequently, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. § 103 should be withdrawn.

Conclusion

Applicants respectfully submit that all of the pending claims are allowable, and request that rejections directed to the claims be withdrawn.

No fee is believed due for this submission. Should any additional fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

by Ricardo J. Moran Reg. # 48,733

Date May 18, 2005

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Enclosures